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Effect of an Enriched Drink on Cognitive Function in Frail Elderly Persons

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Background. Many elderly persons report that they have difficulties learning new things and remembering names, plans, and conversations. Because decreased cognitive function in elderly persons is potentially related to their poor nutritional status, provision of essential nutrients may improve cognitive function. The authors wanted to determine whether consumption of an enriched drink, including moderate doses of all essential micronutrients, improves cognitive function in frail elderly persons.

Methods. Frail, white adults ($n = 101$) who were aged 65 years or older with a body mass index $\leq$25 kg/m^2 were selected for this randomized, double-blind, placebo-controlled trial. They received either an enriched drink or a placebo product for 6 months. Before and after the intervention, participants' cognitive function was assessed (word learning test [WLT], WLT delayed, category fluency [CF] for animals and professions, and recognition memory test for words [RMTW]) and blood biochemical analyses (vitamin B12, homocysteine) were performed.

Results. Sixty-seven residents completed the study period. After 6 months, significant differences were noted in changes of the WLT (0.9 $\pm$ 0.3 vs –0.1 $\pm$ 0.3; $p = .014$) and CF professions (1.2 $\pm$ 0.7 vs –0.6 $\pm$ 0.5; $p = .017$) in the supplement group ($n = 34$) compared with the placebo group ($n = 33$). No significant differences were observed in WLT delayed, RMTW, and CF animals. The plasma vitamin B12 concentration increased (105 $\pm$ 50 vs 8 $\pm$ 16; $p = .003$) and the homocysteine concentration decreased (–6.3 $\pm$ 5.9 vs –0.3 $\pm$ 2.9; $p = .000$) in the supplement group compared with the placebo group.

Conclusions. This study contributes to the evidence that nutritional supplementation may improve neuropsychological performance in frail elderly persons.

MANY elderly persons indicate that their abilities to learn new things (68%) and to remember names (54%), plans (48%), and conversations (35%) have decreased with aging (1). It is estimated that 22% of the community-dwelling elderly is cognitively impaired, and this proportion increases with age (2). Several studies have found that older adults' performances on a variety of psychometric tests decline over time [reviewed by Storandt (3)]. Specifically, declarative memory, a domain of memory associated with conscious recollection and usually assessed with recall or recognition tests, is consistently impaired in elderly persons (4).

Many causes of cognitive impairment exist in elderly persons (2), and impaired nutritional status has been noted as one of them (5). Through epidemiologic studies, the presence of an association between nutrition and cognitive function has become more clear (6,7). These investigations have shown that low intake of nutrients such as thiamin, vitamin B6, vitamin B12, folate (8–12), antioxidants (10,13–15), and specific fatty acids (16) are related to decreased cognitive function.

Low food intake is prevalent in certain groups of elderly persons, with the highest prevalence in elderly persons living in institutions (17). This results in a prevalence of inadequate intake of vitamins B1, B2, B6, and C of 61%, 31%, 58%, and 18%, respectively (17), confirmed by suboptimal biochemical concentrations.

A few supplementation studies focused on improved cognitive function have been performed. Some of these had no placebo treatment (18) or included participants who already had clinical symptoms of cognitive impairment (19–22) or biochemical deficiencies (21,23,24). Only a few studies have been performed in healthy, community-dwelling elderly persons, and the results were contradictory (25,26) or positive but only in those studies in which megadoses of micronutrients were supplied (27–29).

Our aim was to determine, in a well-designed study, whether use of an enriched drink including moderate doses of micronutrients can improve cognitive function in frail elderly persons.

Methods

Study Design

In this randomized, double-blind, placebo-controlled trial, participants received either an enriched drink or a placebo product for 6 months. Before and after the intervention, we assessed cognitive function and performed blood biochemical analyses.

Table 1. Composition of the Dietary Supplement per Daily Dose (250 ml)

Nutrient	Amount
Energy (MJ) (kcal)	1.05 (250)
Protein (whey) (g)	8.75 (14% energy)
Carbohydrates (g)	28.5 (46% energy)
Fat (g)	11.25 (40% energy)
Dietary fiber (g)	4.5
Sodium (mg)	80
Potassium (mg)	550
Chloride (mg)	40
Calcium (mg)	400
Phosphorus (mg)	400
Magnesium (mg)	100
Iron (mg)	9
Zinc (mg)	18
Copper (mg)	3
Manganese (mg)	4
Fluoride (μg)	75
Molybdenum (μg)	40
Selenium (μg)	85
Chromium (μg)	35
Iodine (μg)	150
Vitamin A (μg)	240
Carotenoids (mg)	3
Vitamin D (μg)	13
Vitamin E (mg)	70
Vitamin K (μg)	80
Vitamin C (mg)	250
Vitamin B1 (mg)	1.9
Vitamin B2 (mg)	1.9
Vitamin B6 (mg)	2.5
Vitamin B12 (μg)	5.3
Niacin (mg NE)	14
Pantothenic acid (mg)	4.5
Folate (μg)	480
Biotin (μg)	70
Coenzyme Q10 (mg)	3
Flavonoids (mg)	19

Note: Placebo contains no energy, vitamins, or minerals.

Participants were randomly assigned, in groups of four matched for body mass index (BMI), to receive either nutritional supplementation with a 125-ml enriched drink (containing 30%–150% of the U.S. Recommended Daily Allowance of vitamins and minerals, with enhanced amounts of antioxidants, and containing 250 kcal energy in a daily dose; Table 1) or a noncaloric placebo twice daily between main meals. Participants were randomly assigned to receive either a supplement or a placebo by an independent person not involved in the study. To maximize compliance, participants were visited in their homes every 2 weeks. At that time, they were given additional supplements and any unused packages were counted. Compliance percentages were quantified according to this equation: (number of supplements provided–number of supplements returned) / (number of days participation in study × 2) × 100%. All tests were administered by the same trained investigator before and after 6 months of supplementation.

Participants

We selected frail white persons aged 65 years or older who had a BMI less than 25 kg/m^2 and resided in a home for elderly persons or sheltered housing residence. Residents with cancer, gastrointestinal disease, need for a therapeutic diet incompatible with supplementation, or mental inability to respond to study questions or to remember taking the supplement were not eligible to participate. Participants were enrolled between May 1999 and March 2001. The medical ethics committee of Wageningen University, The Netherlands, approved the study. Participants gave written informed consent before randomization.

Participant characteristics.—Age, sex, education, the number of prescribed medicines, diagnosed chronic diseases, and visual impairment were recorded.

Dietary intake.—A 3-day estimated dietary record was collected (30). We calculated food intake using standard portion sizes using the computerized 1997 Dutch Food Composition Table (31).

Blood sampling.—Venous blood samples were collected in the participants' homes in coagulation tubes (vitamin B12) or heparin-prepared tubes (homocysteine) at baseline and at the end of the study. The participants had fasted overnight and were in a sitting position. Samples were cooled immediately and centrifuged within 4 hours at 2500*g* for 10 minutes at 4°C. Plasma (homocysteine) or serum (vitamin B12) was removed and stored at –80°C for batch analysis at the end of the study.

Biochemical measurements.—Plasma homocysteine was measured using high-powered liquid chromatography according to the method of Daskalakis and coworkers (32). Serum vitamin B12 was analyzed for a selected group of 26 participants, for whom leftover serum samples were available, using ion capture Im_x (Abbott Laboratories, Abbott Park, IL) (33). Concentrations greater than 221 pmol/l were considered normal (34). Analyses were performed at the Department of Clinical Chemistry, University Medical Center St. Radboud, Nijmegen (vitamin B12) and the Department of Analytical Chemistry, Numico Research, Wageningen, The Netherlands (homocysteine).

Anthropometric measurements.—Anthropometric measurements were performed with participants wearing light clothing without shoes and after emptying their bladders. Body weight was measured to the nearest 0.1 kg using a calibrated scale (Seca, Hamburg, Germany). Knee height was measured to the nearest 0.1 cm using a stadiometer to estimate participant height. Body mass index was calculated as weight / (knee height^2 × 10) (35).

Mini-Mental State Examination (MMSE).—The Mini-Mental State Examination was performed according to the method of Folstein and colleagues (36). A maximum score of 30 points for persons in good mental state can be achieved (37), and a cutoff score of 23 was used to define cognitive impairment (38). The version including the serial sevens form was selected (39).

Geriatric Depression Scale.—The short version of the geriatric depression scale for affective capacity was applied

Table 2. Baseline Parameters of Frail Elderly Participants in the Supplementation Study (Means ± *SD*)

Parameter	Placebo	Supplement
N	33	34
Age (y)	81 ± 7	84 ± 6
Female (%)	53	62
BMI (kg/m^2)	24.1 ± 2.3	23.5 ± 2.4
Energy intake (kJ/d)*	6818 ± 1210	7133 ± 1636
Energy intake (kcal/d)	1623 ± 289	1700 ± 392
Intake of vitamin B1 (mg/d)*	0.94 ± 0.77	1.04 ± 0.94
Intake of vitamin B2 (mg/d)*	1.23 ± 0.37	1.19 ± 0.35
Intake of vitamin B6 (mg/d)*	1.13 ± 0.28	1.11 ± 0.33
Intake of vitamin B12 (μg/d)*	3.59 ± 1.50	3.71 ± 2.35
Intake of folate (μg/d)*	203 ± 52.7	182 ± 61.2
GDS >5 (%)	3.7 ± 2.5 (21)	3.3 ± 2.4 (12)
MMSE ≤23 (%)	26 ± 3 (21)	26 ± 3 (24)
Education (%)		
≤6 years	38	50
7–9 years	47	35
>9 years	15	15
Impaired vision	1/33	4/34
No. of chronic diseases	1.6 ± 1.1	2.0 ± 1.4
No. of medications	3.6 ± 2.8	4.2 ± 3.7

Notes: *$n = 25 + 27$ for both groups.

GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination; BMI = body mass index.

(40,41). Participants were classified as depressed if they had a score of 5 or more.

Neuropsychological Tests

Word learning test (WLT).—The Dutch version of the 15-word learning test was administered (Department of Neuropsychology, University of Groningen, The Netherlands). Fifteen words were read to the participants, who were then asked to repeat as many words as possible (immediate recall). This was repeated five times, and then delayed recall (WLT delayed) was tested after the participants performed nonstrenuous, non-neuropsychological tests for 10 minutes. The total number of correct words of the five repetitions was summed and divided by the number of repetitions (for a maximum score of 15). Delayed recall was scored as the total number of correct words (for maximum score of 15).

Category fluency (CF) test.—Two category fluency tests were administered in which the participants were asked to name, within 60 seconds, as many animals or professions as they could (42,43).

Recognition memory test for words (RMTW).—The Dutch version of the RMTW, as described by Diesfeldt (44), was used. After hearing 50 words, each spaced by 3 seconds, the participants were asked to recognize the words from 50 pairs including a correct word and a distractor (for a maximum score of 50).

Statistical Analyses

Values mentioned are means ± standard deviations for descriptives and means ± standard error of the mean for changes. We compared the characteristics and baseline neuropsychological scores of the supplement and control groups using the two-sided Student *t* test, chi-squared test, and the Wilcoxon signed rank test (if not normally distributed according to the Kolmogorov Smirnov test: WLT delayed, CF animals). We compared the changes in neuropsychological scores in both trial groups using the one-sided Student *t* test, because we hypothesized improved cognitive function in the supplement group. We performed post hoc tests using paired *t* tests. Probability values less than .05 were considered significant. We calculated effect size (ES) as the mean change/standard deviation (45). We analyzed the data using SPSS version 10.0 for Windows (SPSS, Chicago, IL).

RESULTS

Baseline Characteristics and Study Compliance

One hundred one residents were randomized, of whom 34 dropped out during the study period. Figure 1 shows a participant flow chart. Intention-to-treat analyses of the 101 residents using last observation carried forward analysis for outcome variables did not differ from analyses of participants who completed the study. Data reported are thus from residents for whom complete data for the study period were obtained. Baseline characteristics were similar in the group that completed the study period and the group that dropped out, except for the MMSE scores, which were significantly less in the participants who dropped out. High compliance was observed for the supplement group (88% ± 23%) and for the placebo group (94% ± 14%).

Table 2 reports baseline characteristics, of which none was significantly different. Twenty-three percent of participants had a score of 23 or less on the MMSE. Sixteen percent had a score higher than 5 on the Geriatric Depression Scale. The proportions of participants with a vitamin intake less than two thirds of the U.S. Recommended Daily Allowance (2001) (46) were 36% for vitamin B1, 11% for vitamin B2, 53% for vitamin B6, 10% for vitamin B12, and 15% for folate.

Neuropsychological Tests

Table 3 shows the neuropsychological scores at baseline and follow-up. Scores for the WLT (ES = 0.43) and CF professions (ES = 0.44) improved significantly during the study period in the supplement group ($n = 34$) compared with the placebo group ($n = 33$). We found no significant differences for changes between groups in WLT delayed (ES = 0.20), RMTW (ES = –0.39), and CF animals (ES = 0). The supplement group had significantly lower baseline WLT and WLT delayed scores. Paired *t* tests indicated a significant increase in scores in the supplement group for WLT, WLT delayed, CF professions, and CF animals but not for RMTW. No significant changes occurred in the placebo group.

Plasma Vitamin B12 and Homocysteine

We found a significant increase in vitamin B12 concentration and a decrease in homocysteine concentration in the supplement group during the study period. Concentrations remained similar in the placebo group. This resulted

Table 3. Mean Scores on Memory Tests at Baseline and Changes After 6 Months of Nutritional Supplementation in Frail Elderly Persons Receiving Placebo ($n = 33$) or Supplement ($n = 34$)

	Baseline (Mean ± *SD*)		Change (Mean ± *SEM*)			
Test	Placebo	Supplement	Placebo	Supplement	*p*	95% CI
Neuropsychological tests						
WLT	6.1 ± 2.2	4.4 ± 2.1*	−0.1 ± 0.3	0.9 ± 0.3	0.014	−1.71
WLT delayed[†]	6.6 ± 2.1	4.7 ± 2.8*	0.3 ± 0.4	0.9 ± 0.4	0.152	−1.85
RMTW[‡]	40.9 ± 5.5	40.3 ± 4.9	0.7 ± 1.2	−1.1 ± 0.9	0.383	−1.19
Category fluency animals	15.2 ± 4.3	13.9 ± 4.5	0.9 ± 0.7	0.9 ± 0.6	0.473	−1.88
Category fluency professions	11.9 ± 3.4	10.1 ± 4.3	−0.6 ± 0.5	1.2 ± 0.7	0.017	−3.46
Biochemistry						
Plasma homocysteine (μmol/L)[§]	17.6 ± 5.0	18.4 ± 7.9	−0.3 ± 2.9	−6.3 ± 5.9	0.000	—
Plasma vitamin B12 (pmol/L)[‖]	290 ± 99	304 ± 118	−8 ± 16	105 ± 50	0.003	—

Notes: * $p < .01$ versus placebo.
[†] $n = 27$ for both groups.
[‡] $n = 30$ for placebo; $n = 28$ for supplement.
[§] $n = 23$ for placebo; $n = 2$ for supplement, nonparametric test.
[‖] $n = 14$ for placebo; $n = 12$ for supplement, nonparametric test.
WLT = Word learning test; RMTW = recognition memory test for words.

in a significant difference between groups during the study period.

Discussion

We observed a significant improvement on two tests of cognitive function (WLT and CF professions) after 6 months of consumption of an enriched drink by frail elderly persons.

The population we selected were elderly persons living in homes for the elderly or sheltered residences who could respond to study questions and who would not forget to consume the daily supplement. Although they were not severely cognitively impaired, the presence of persons with mild cognitive impairment or dementia cannot be excluded, because it can be present at an early stage without being diagnosed, which is suggested by the 23% of participants with low MMSE scores. Potential participation of persons with very high or very low cognitive function was relatively low, so our pool of participants had intermediate cognitive function. The final mean MMSE score in our study population is comparable to scores found in the general elderly population (mean MMSE, 26 points) (38), slightly higher than the average found in residences for the elderly (mean MMSE, 20) (18), elderly persons living in service flats (mean MMSE, 23) (47), and frail elderly persons living in their own homes (mean MMSE, 20) (48), but it was lower than in healthy elderly persons (mean MMSE, 28–29) (49,50). Chandra (25) observed a lower MMSE score in persons with a plasma deficiency of one or more vitamins compared with those who were not deficient. A significant proportion of our participants had low intakes of vitamins, and the average homocysteine concentration [which can be considered an indicator of impaired status of vitamin B6, vitamin B12, and folate (51)] in our population was greater than in other studies of community-dwelling elderly persons (26,34,52). This supports the assumption that our population is at risk for subclinical deficiency and therefore could benefit from vitamin supplementation.

Because plasma homocysteine concentrations are related to cognitive function (53,54), we measured changes in homocysteine levels as a biochemical variable in addition to the cognitive tests. Indeed, besides the improvement in cognitive tests we found a significant decrease in plasma homocysteine concentrations. Our data support the efficacy of relatively low-dose oral micronutrient supplementation for decreasing homocysteine concentrations in elderly persons, as found in previous studies in other groups of elderly persons (26,55). However, changes in antioxidant levels may also have contributed to the improvements we found in the participants' neuropsychological test scores.

The tests we used were representative of the typical areas of cognitive decline in elderly persons (1,56,57). Verbal fluency reflects frontal lobe and language function (58), and studies have suggested that vitamin B12 deficiency may be associated with frontal lobe damage (59). Antioxidant levels appear to be related to the same tests of semantic memory, free recall, and recognition (15). Previous supplementation studies showed that the tests we used were sensitive to improvements (24).

We used the same test versions at both measurement times, because we did not expect the presence of a learning effect after such a long time. Furthermore, the study was placebo controlled. Paired analysis in the placebo group indeed showed no significant changes during the study period for any of the neuropsychological tests. This corresponds with observations by Chandra (25) during a 1-year period.

The score on the WLT is a measure of short-term memory, and the delayed score is a measure of intermediate memory (60). The absolute scores on the WLT in our population were much lower than in healthy elderly persons with a mean age of 81 years (61). The effect sizes we found on the WLT and CF professions can be considered small to medium according to the classification of Cohen (45). This means that the results are, from a statistical perspective, substantial and indicate possible clinical relevance.

The fact that the participants' baseline scores on two of the neuropsychological tests were not well matched for our groups may affect the interpretation of our results. However,

scores in the placebo group were not as high to preclude improvement; rather, the lower scores in the supplement group may have risked to preclude improvement. Subtle changes in cognitive function can be difficult to measure, because more severely affected persons probably will not have improvement on neuropsychological tests. A possible explanation for this could be that restoration of the transmethylation capacity with increased synthesis of neurotransmitters could contribute to the beneficial effect of vitamin substitution. Persons with mild to moderate dementia may have better preserved neuronal function and are more likely to respond clinically to vitamin substitution than would persons with severe dementia (21). As also indicated by the MMSE scores, we did not include such a severely impaired group, and the scores in the supplement group did increase during the study period. Chandra (25) observed that those persons whose baseline plasma values were low and responded to supplementation had a greater improvement in cognition. This may have been the case for our supplement group, in whom we found low plasma concentrations of several vitamins.

This study contributes to the evidence that nutritional supplementation may improve neuropsychological performance in frail elderly persons. From the effect sizes we obtained we may infer that our results are clinically relevant.

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